71. (New) The compound of claim 1 wherein carbamyl is C_1-C_6 alkyl carbamyl.

72. (New) The compound of claim 1 wherein carboxyl is selected from the group consisting of C_1-C_6 alkyl carboxyl and phenyl esters.

B11 Cancelled

73. (New) The composition of claim 47 wherein amido is selected from the group consisting of primary, C_1-C_6 alkyl, phenyl secondary and tertiary amido.

74. (New) The composition of claim 47 wherein carbamyl is C_1-C_6 alkyl carbamyl.

75. (New) The composition of claim 47 wherein carboxyl is selected from the group consisting of C_1-C_6 alkyl carboxyl and phenyl esters.

REMARKS

Claims 2-3, 7, 17-18, 21-22, 24-46, 48-49, 53, 63-64, and 67-68 have been cancelled without prejudice to the filing of continuing applications. Claims 1, 15, 20, 47, and 60 have been amended to further clarify the invention, and new claims 70-75 added. Support for the amendments is found throughout the specification, for instance, in Examples 1-54. With these amendments, the pending claims are 1, 4-6, 8-16, 19-20, 23, 47, 50-52, 54-62, 65-66, and 69-75. No new matter has been added by these amendments.

Turning to the Office Action, the specification stands objected to as containing a "URL"; claim 47 stands rejected under 35 U.S.C. § 112, first paragraph, as not being enabled; claims 1, 4-6, 8-16, 19, 20, 23, 47, 50-52, 54-62,

65, 66 and 69 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite; and claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by WO 97/30072 ("Majer"). The Office has also required the Applicants to file sequence disclosures in compliance with 37 C.F.R. 1.821 through 1.825.

The specification has been amended to delete the URL, thus removing the grounds for the objection. The claims have been amended to limit them to the elected Group. Finally, enclosed are sequence listings for the amino acid sequences disclosed in the specification, in compliance with 37 C.F.R. 1.821 through 1.825. The remaining Office Action rejections are addressed below.

The 35 U.S.C. § 112, First Paragraph, Rejection

Claim 47 stands rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. The Office contends that the term "pharmaceutical" composition implies therapeutic efficacy and that this is not in evidence. The Office goes on to provide text for a *method* claim relating to inhibiting the formation of amyloid beta protein, which the Office states may be enabled. The relevance of the suggested method claim to claim 47, which is a composition claim, is not understood by Applicants and further clarification is requested. Finally, at page 3 of the Office Action, the Office states that the rejection can be overcome by deleting the term "pharmaceutical" from the first line of claim 47. Applicants respectfully traverse this rejection.

The use of the term "pharmaceutical" in composition claims has long been accepted and is widely practiced. For instance, a search of the United States Patent and

Trademark Office's patent database reveals that *over 13000* U.S. patents containing the phrase "a pharmaceutical composition" in the claims have issued since 1996 alone. The language is merely used to define the scope of the type of compositions of matter that are encompassed by the claims, i.e., pharmaceutical type compositions. The term does not introduce issues of therapeutic efficacy.

Thus here, the "pharmaceutical" terminology is consistent with long accepted patent practice and does nothing more than identify the types of compositions that are encompassed by the claims. The phrase does not relate to "therapeutic efficacy" and its use in claim 47 should not have elicited a § 112 rejection. Withdrawal of the § 112 rejection of claim 47 is therefore respectfully requested.

The 35 U.S.C. § 112, Second Paragraph, Rejection

Claims 1, 4-6, 8-16, 19, 20, 23, 47, 50-52, 54-62, 65, 66 and 69 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Office's rejections under this section are addressed by the present amendment or by the comments below. The amendments do not narrow the scope of the claims and serve only to clarify the invention.

In response to the Office's objection to the terminology "including" in claim 1, the substituents following this term have been removed and introduced as new dependent claims, or the claim has otherwise been amended. "Carbamyl esters" has been replaced with "carbamic acid esters," and "phenyl amides" replaced with "benzamides," the replacements being the more widely accepted terminology for these types of substituents. Claim 1 has also been

amended to add a hydrogen to the nitrogen which is bonded to the A group, and to replace "heterocyclylic" with "heterocyclic." Analogous amendments were made to composition claim 47.

In claim 15, "Bis" was replaced with "B is," as suggested by the Office.

In claim 20, "according to claim 15" has been replaced with "according to claim 5." This amendment corrects a typographical error.

Regarding the Office's suggestion that the clarity of claim 47 would be improved by amending the first line of the claim (namely to replace "pharmaceutical composition" with "composition" and "pharmaceutically acceptable diluent"), Applicants' respectfully point the Office's attention to the above arguments in response to the § 112, first paragraph, rejection of this claim. Thus, Applicants respectfully submit that the "pharmaceutical" terminology of the claim is consistent with long accepted terminology, and therefore decline to amend the claim in the manner proposed by the Office.

In view of the above amendments and discussion, withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of claims 1, 4-6, 8-16, 19, 20, 23, 47, 50-52, 54-62, 65, 66 and 69 is respectfully requested.

The 35 U.S.C. § 102(b) Rejection

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Majer. The Office contends that the claim is anticipated by compound 6 (page 37) of the reference when "A" is t-butyloxycarbonyl, "B" is OMe, R1 is isopropyl and R2 is benzyl in Applicants' Formula I. Office Action, page 5. The Office states that although

Claim 1 does not specifically disclose that A can be t-butyloxycarbonyl (t-Boc), claim 1 does disclose that A can be alkylacyloxy or carboxyalkyloxy, either of which could encompass tBoc. Office Action, page 5.

The alkylacyloxy and carboxyalkyloxy groups belong to a non-elected definition of the substituent A. The non-elected A substituents have been cancelled from the instant claims and reserved for prosecution in continuing applications. Thus, although Applicants do not agree with the Office's position that claim 1 is anticipated by the reference, the bases of the rejection are now moot in view of the instant claim amendment. Accordingly, withdrawal of the 35 U.S.C. § 102(b) rejection of claim 1 is respectfully requested.

CONCLUSION

Applicants respectfully submit that the pending claims are allowable. Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited.

Respectfully submitted,

Dated: October 25, 2002 By: _____

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Marked Up Copy of Amended Paragraphs

The paragraph at page 32, line 4:

Scheme III illustrates the synthesis of aryl-substituted statine analogs via Weinreb amide formation and reduction followed by addition of a chiral enolate to give a diastereoselective product in a ratio of 7:1 of the desired isomer. This scheme can be generalized to make a variety of derivatized statine valine dimers with varying C- and N-terminal groups by selection of different stating materials and intermediates. For example, the aryl statine derivative may be varied by selecting a different arylmethylene aminoacid as a starting material. All of the aryl amino acids used to form a derivatized aryl-statine were commercially available, and obtained from Synthetec, Inc. Monmouth Junction, New Jersey[, (www.synthetech.com)].

The paragraph at page 51, line 5:

This test compound was prepared by coupling commercially available 2-carboxy-diphenylether with the peptide 3,5-difluoroPhe/Sta-Val-Ala-Glu-Phe [SEQ ID NO:1] according to the standard EDC coupling procedures. The VAEF [SEQ ID NO:2] peptide sequence was previously established to possess inhibitory binding capability at the active site of the enzyme.

The paragraph at page 51, line 23:

The geminal dimethyl analog of 32 was prepared as in Example 31, but using the 3,3-demethylglutaric anhydride. This groups was coupled to the derivatized Sta-Val-Ala-Glu-

Phe [SEQ ID NO:3] pentapeptide and assayed for binding affinity in the enzyme system.

The paragraph at page 52, line 4:

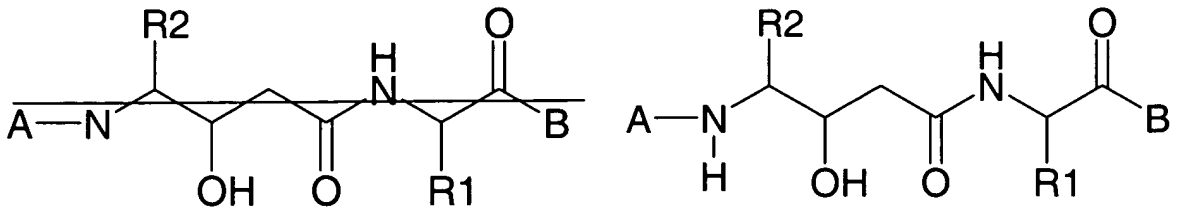
Glutaric anhydride was treated with methanol to provide the mono methyl ester, which was treated with phosgene to produce the mono methyl ester with the opposite end being the acid chloride. The acid chloride was treated with piperidine to form the amide. The methyl ester was then hydrolyzed to the free acid and coupled with the derivatized Sta-Val-Ala-Glu-Phe [SEQ ID NO:3] pentapeptide.

The paragraph at page 57, line 18:

4-methylcinnoline is oxidized to 4-carboxycinnoline and then coupled to the 3,5-difluoroPhe/Sta-Val-Ala-Glu-Phe [SEQ ID NO:1].

Marked Up Copy of Amended Claims

1) (Twice amended) A compound of formula 1

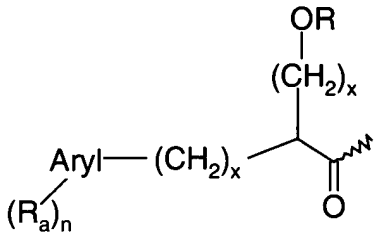


Formula 1

wherein:

A is

[i]



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

each x is independently 0, 1 or 2;

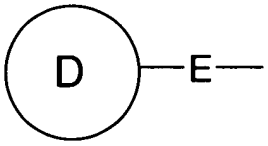
R is H, C_1-C_6 alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH_2OH, -CO_2H, -CF_3, Cl, Br, F; and C_1-C_2 alkyl;

each R_a is independently selected from the group consisting of H, OH, C_1-C_3 alkyl; C_1-C_6 alkylacylamino, C_1-C_6

alkylacyloxy, C_1-C_6 alkyloxy, C_1-C_6 alkylthioxy, amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary), NH_2, mono and di(C_1-C_6 alkyl and phenyl) amino, carbamyl (including C_1-C_6 alkyl and phenyl amides and esters), carboxyl (including C_1-C_6 alkyl and phenyl esters), carboxy(C_2-C_5)alkyloxy and N-heterocyclylacyl;

and n is 1 or 2;

ii)]



wherein D is chosen from aryl having 5 to 6 atoms[,]; [optionally including up to] heteroaryl having 5 to 6 atoms where 1 or 2 heteroatoms are selected from [the] N, O, and S; fused aryl of 8 to 14 atoms; [optionally including up to] fused heteroaryl of 8 to 14 atoms where 1, 2, or 3 heteroatoms are selected from [the] N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms [including up to] where 1, 2, or 3 heteroatoms are selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C_1-C_8) alkyloxyaryl;

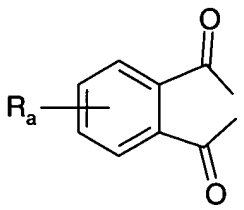
and wherein E is a divalent group chosen from carbonyl, sulfonyl, C_1-C_3 alkylene, -X- (C_1-C_3) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C_1-C_3 alkyl; C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy, C_1-C_6 alkyloxy, C_1-C_6 alkylthioxy, amido [(including primary, C_1-C_6 alkyl and phenyl secondary and tertiary)], NH_2, mono and di(C_1-C_6 alkyl and phenyl) amino,

carbamyl, benzamides [(including C_1-C_6 alkyl and phenyl amides and esters)], carbamic acid esters, carboxyl [(including C_1-C_6 alkyl and phenyl esters)], carboxy(C_2-C_5)alkyloxy, N-heterocyclylacyl, C_1-C_3 alkylsulfonyl, sulfonamide and C_1-C_3 alkylsulfonamide;

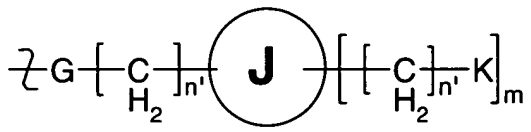
[iii) C_1-C_6 alkanoyl; C_2-C-$_6$ alkenoyl; and methylthioC_1-C_5 alkanoyl, any of which may be substituted with up to two groups chosen from OH, C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy; C_1-C_6 alkyloxy; C_1-C_6 alkylthioxy, amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary), amino, C_1-C_6 alkyl and phenyl amino, carbamyl (including C_1-C_6 alkyl and phenyl amides and esters), carboxyl (including C_1-C_6 alkyl and phenyl esters), carboxy(C_2-C_5)alkyloxy and N-heterocyclylacyl, C_1-C_3 alkylsulfonyl, sulfonamide and C_1-C_3 alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and Ra is as defined above;]

B is selected from -OH; C_1-C_6 alkyl or C_1-C_6 alkyl amino, di(C_1-C_6 alkyl)amino, C_1-C_6 alkyloxy, [N-heterocyclylic] N-heterocyclic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

and G is [N] NH or O;

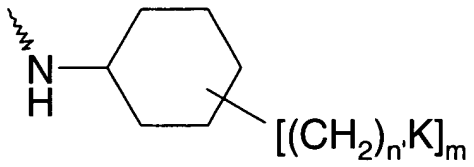
J is selected from the group consisting of aryl having a 5 to 6 membered ring; [optionally including up to] aryl having a 5 to 6 membered ring with 1, or 2 heteroatoms selected from [the] N, O, and S; fused aryl rings of 8 to 14 atoms; [optionally including up to] fused aryl rings of 8 to 14 atoms with 1, 2, or 3 heteroatoms selected from N, O, and S[,]; mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms [including up to] with 1, 2, or 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C_1-C_3 alkyl; C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy, C_1-C_6 alkyloxy, C_1-C_6 alkylthioxy, amido [(including primary, C_1-C_6 alkyl and phenyl secondary and tertiary)], NH_2, mono and di(C_1-C_6 alkyl and phenyl) amino, carbamyl [(including C_1-C_6 alkyl and]; phenyl amides [and esters)], carbamates, carboxyl [(including C_1-C_6 alkyl and phenyl esters)] and carboxy(C_2-C_5)alkyloxy;

R1 is straight or branched chain C_1-C_5 alkanyl or C_2-C_5 alkenyl;

R2 is C_{1-5} straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C_{1-3} alkyl, trifluoromethyl or halogen, and stereoisomers, hydrates or pharmaceutically acceptable salts thereof.

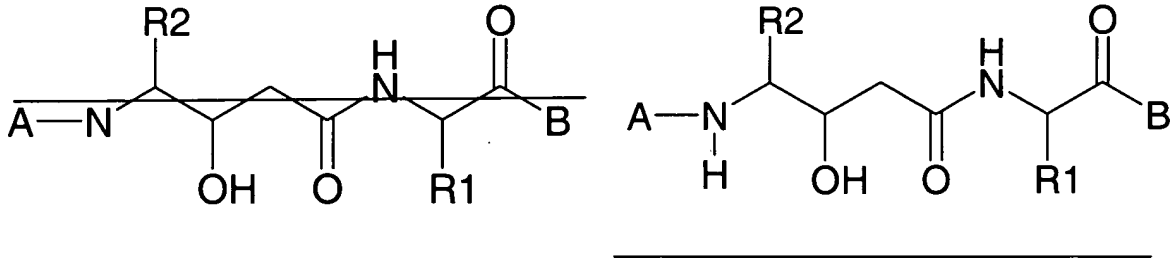
15) (Amended) The compound of claim 1 wherein [Bis] B is



wherein K, n' and m are as defined in claim 1.

20) (Amended) The compound of claim 1 wherein A is selected according to claim [15] 5 and B is selected according to claim 15.

47) (Twice amended) A pharmaceutical composition comprising a compound of formula 1

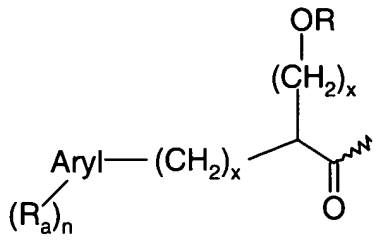


Formula 1

wherein:

A is

[i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

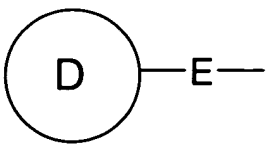
each x is independently 0, 1 or 2;

R is H, C_1-C_6 alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; $-CH_2OH$, $-CO_2H$, $-CF_3$, Cl, Br, F; and C_1-C_2 alkyl;

each R_a is independently selected from the group consisting of H, OH, C_1-C_3 alkyl; C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy, C_1-C_6 alkyloxy, C_1-C_6 alkylthioxy, amido (including primary, C_1-C_6 alkyl and phenyl secondary and tertiary), NH_2, mono and di(C_1-C_6 alkyl and phenyl) amino, carbamyl (including C_1-C_6 alkyl and phenyl amides and esters), carboxyl (including C_1-C_6 alkyl and phenyl esters), carboxy(C_2-C_5)alkyloxy and N-heterocyclylacyl;

and n is 1 or 2;

ii)]



wherein D is chosen from aryl having 5 to 6 atoms[,]; [optionally including up to] heteroaryl having 5 to 6 atoms where 1 or 2 heteroatoms are selected from [the] N, O, and S; fused aryl of 8 to 14 atoms; [optionally including up to] fused heteroaryl of 8 to 14 atoms where 1, 2, or 3 heteroatoms are selected from [the] N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms [including up to] where 1, 2, or 3 heteroatoms are selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C_1-C_8) alkyloxyaryl;

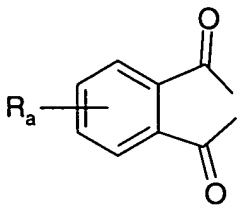
and wherein E is a divalent group chosen from carbonyl, sulfonyl, C_1-C_3 alkylene, -X- (C_1-C_3) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH, C_1-C_3 alkyl; C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy, C_1-C_6 alkyloxy, C_1-C_6 alkylthioxy, amido [(including primary, C_1-C_6 alkyl and phenyl secondary and tertiary)], NH_2, mono and di(C_1-C_6 alkyl and phenyl) amino, carbamyl, benzamides [(including C_1-C_6 alkyl and phenyl amides and esters)], carbamic acid esters, carboxyl [(including C_1-C_6 alkyl and phenyl esters)], carboxy(C_2-C_5)alkyloxy, N-heterocyclylacyl, C_1-C_3 alkylsulfonyl, sulfonamide and C_1-C_3 alkylsulfonamide;

[iii) C_1-C_6 alkanoyl; C_2-C-$_6$ alkenoyl; and methylthioC_1-C_5 alkanoyl, any of which may be substituted with up to two groups chosen from OH, C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy; C_1-C_6 alkyloxy; C_1-C_6 alkylthioxy, amido (including primary, C_1-C_6 alkyl and phenyl secondary and

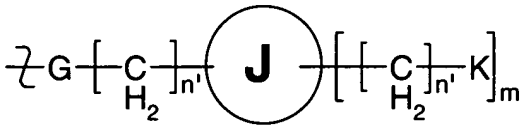
tertiary), amino, C_1-C_6 alkyl and phenyl amino, carbamyl (including C_1-C_6 alkyl and phenyl amides and esters), carboxy(C_2-C_5)alkyloxy and N-heterocyclylacyl, C_1-C_3 alkylsulfonyl, sulfonamide and C_1-C_3 alkylsulfonamide;

and iv) a divalent group of the formula:



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and Ra is as defined above;]

B is selected from -OH; C_1-C_6 alkyl or C_1-C_6 alkyl amino, di(C_1-C_6 alkyl)amino, C_1-C_6 alkyloxy, [N-heterocyclylic] N-heterocyclic and



each n' is independently 0, 1 or 2;
m is 0, 1, 2 or 3;
and G is [N] NH or O;
J is selected from the group consisting of aryl having a 5 to 6 membered ring; [optionally including up to] aryl having a 5 to 6 membered ring with 1, or 2 heteroatoms selected from [the] N, O, and S; fused aryl rings of 8 to

14 atoms; [optionally including up to] fused aryl rings of 8 to 14 atoms with 1, 2, or 3 heteroatoms selected from N, O, and S[,]; mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 5 to 12 carbon atoms [including up to] with 1, 2, or 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C_1-C_3 alkyl; C_1-C_6 alkylacylamino, C_1-C_6 alkylacyloxy, C_1-C_6 alkyloxy, C_1-C_6 alkylthioxy, amido [(including primary, C_1-C_6 alkyl and phenyl secondary and tertiary)], NH_2, mono and di(C_1-C_6 alkyl and phenyl) amino, carbamyl [(including C_1-C_6 alkyl and]; phenyl amides [and esters)], carbamates, carboxyl [(including C_1-C_6 alkyl and phenyl esters)] and carboxy(C_2-C_5)alkyloxy;

R1 is straight or branched chain C_1-C_5 alkanyl or C_2-C_5 alkenyl;

R2 is C_{1-5} straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C_{1-3} alkyl, trifluoromethyl or halogen,
[and] and pharmaceutically acceptable salts and esters thereof and a pharmaceutically acceptable diluent.

60) (Amended) The composition of claim 47 wherein B is selected from the group consisting of -OH, C_1-C_6 alkoxy, mono and di(C_1-C_6) alkylamino, aminoC_1-C_4 alkyl-p-benzoic acid and C_1-C_6 alkyl and phenyl esters thereof, and N-heterocyclic.